REMARKS

Upon entry of the amendment, claims 27-38 are pending in this application. Claims 1-16 were previously cancelled and claims 17-26 are cancelled in this paper, without prejudice to or disclaimer of the subject matter contained therein. Claims 27-38 have been newly added.

The amendments are solely for advancing prosecution. Applicants, by amending or cancelling any claims herein, make no admission as to the validity of any rejection made by the Examiner against any of these claims. Applicants reserve the right to reassert the original claim scope of any claim amended herein, in a continuing application.

New claim 27 recites "a method for enhancing transduction efficiency of a recombinant virus into a cell, comprising contacting the recombinant virus with the cell, wherein the recombinant virus comprises a relaxin-encoding nucleotide sequence operatively linked to a regulatory sequence directing its expression and the relaxin protein expressed thereby enhances transduction of the recombinant virus." Support for the claim can be found throughout the specification and the drawings as originally filed, including, for example, Figures 3 and 4.

New claim 33 recites "a method for enhancing apoptosis in a tumor cell, comprising contacting a recombinant virus with the tumor cell, wherein the recombinant virus comprises a relaxin-encoding nucleotide sequence operatively linked to a regulatory sequence directing its expression, and the relaxin protein

expressed thereby enhances apoptosis in the tumor cell." Support for the claim can be found throughout the specification and the claims as originally filed, including, for example, Table 1.

The Drawings are amended to replace Figures 3 and 4 with the same but in color. Replacement Drawings of Figures 3 and 4 in color drawings are submitted herewith, along with a petition under 37 C.F.R. §1.84(a)(2).

The Specification has been amended to incorporate the language required for submission of color drawings under 37 C.F.R. § 1.84(a)(2)(iii).

No new matter has been introduced to this application within the meaning of 35 U.S.C. §132.

In view of the following, further and favorable consideration is respectfully requested.

I. Rejections of Claims 17-23 under 35 USC §102(b) and §102(e)

The Examiner has rejected claims 17-23 under 35 USC §102(b) and §102(e) as being anticipated by *Hirsch et al.* (U.S. Publication No. 2003/0003583). As the basis for the rejection, the Examiner asserts that *Hirsch et al.* disclose adeno-associated viral vectors for transduction of a target gene (abstract) wherein the target gene may be relaxin (0140). The Examiner further asserts that *Hirsch et al.* disclose a method of delivering a gene into cells for the treatment of cancer (0151), the method comprising the use of an adenoviral gene delivery system (0019), wherein the gene may encode relaxin (0140).

Claims 17-23 have been cancelled making the rejections *moot*. Presently pending claims 27-38 are not anticipated by *Hirsch et al.*

The test for anticipation under 35 USC §102(a) is whether each and every element as set forth is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987); MPEP §2131. The identical invention must be shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989); MPEP §2131. The elements must also be arranged as required by the claim. *In re Bond*, 15 USPQ2d 1566 (Fed. Cir. 1990). Moreover, the rule of law requires that the Examiner must consider a reference in its entirety in determining the scope and content of the reference. *W.L. Gore & Assocs., Inc. v. Garlock, Inc.,* 721 F.2d 1540, (Fed. Cir 1983), *cert. denied*, 469 U.S. 851 (1984). Thus, the Examiner must acknowledge any disclosure in the reference that teaches away from the present invention. *Id.*

Further, subject matter is only inherent when extrinsic evidence makes it clear that the subject matter is necessarily present in (i.e., necessarily flows from) the disclosure of cited art, and that ordinarily skilled artisans would recognize it. MPEP §2112. Ordinarily skilled artisans however need not recognize this presence at the time of invention. MPEP §2112(II). Inherency cannot be established by mere possibilities or even probabilities. The fact that a certain result or characteristic may occur or may be present in cited art is <u>not</u> sufficient to establish the inherency of that result or characteristic. MPEP §2112 (IV), citing *In*

re Rijckaert, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) reversing a rejection based on inherency because result due to optimization of conditions was not necessarily present in the prior art.

Presently Claimed Subject Matter

Claim 27 is directed to a method for enhancing transduction efficiency of a recombinant virus into a cell, comprising contacting the recombinant virus with the cell, wherein the recombinant virus comprises a relaxin-encoding nucleotide sequence operatively linked to a regulatory sequence directing its expression and the relaxin protein expressed thereby enhances transduction of the recombinant virus. Claims 28-32 are, directly or indirectly, dependent from claim 27, and thus contain all the elements of claim 27 as noted above.

Claim 33 is directed to a method for enhancing apoptosis in a tumor cell, comprising contacting a recombinant virus with the tumor cell, wherein the recombinant virus comprises a relaxin-encoding nucleotide sequence operatively linked to a regulatory sequence directing its expression, and the relaxin protein expressed thereby enhances apoptosis in the tumor cell. Claims 34-38 are, directly or indirectly, dependent from claim 33, and thus contain all the elements of claim 33 as noted above.

Accordingly, all of the pending claims require the method where ***the expressed relaxin protein enhances transduction of the recombinant virus into a cell, or enhances apoptosis in the tumor cell***.

Applicants submit that, as described in the specification, e.g., at page 3, lines 7-20, page 5, lines 10-20, and page 6, line 26 to page 7, line 6, the present subject matter is based on the discovery that relaxin can ***dramatically improve the transduction efficiency*** of a gene delivery system. The expressed relaxin protein induces the degradation of collagen, a major component of extracellular matrix surrounding cells, to disrupt connective tissue and basal membrane, thereby resulting in the degradation of extracellular matrix. This successive action is believed one of mechanisms underlying the improvement of ransduction efficiency by relaxin, which is evidently verified by the examples in the specification.

Hirsch et al.

Hirsch et al. describe methods for using adeno-associated virus for transduction of a target gene in a variety of tissues wherein the expression of the transgene is regulated by "administration of a proteasome inhibitor." *Hirsch et al.* further describe that a therapeutic gene can be delivered *in vivo* by an adeno-associated virus to a tissue that is not normally transduced by adeno-associated virus; the host would then be administered a proteasome inhibitor in order to induce "expression of the therapeutic gene." *Hirsch et al.* also describe that the proteasome inhibitor is administered only when gene expression is desired (*see* paragraphs [0008] to [0010]). With regard to the target gene, *Hirsch et al.* generally describe a wide variety of genes that may be employed for the method

disclosed therein at paragraph [0138] through paragraph [0141], one of them being relaxin.

Accordingly, Applicants submit that *Hirsch et al.* teach that the ***expression*** of relaxin gene, if it is contained in the AAV (adeno-associated virus) disclosed therein, is regulated by the "***administration of a proteasome inhibitor***." The key feature of the AVV of *Hirsch et al.* exists in the point that the induction of a therapeutic gene expression in the recombinant AAV is conducted by the administration of a proteasome inhibitor. The method of *Hirsch et al.* to deliver a selected gene to a cell and to regulate its expression is therefore accomplished only when the cell or tissue is contacted with a proteasome inhibitor.

However, as Applicants previously argued, *Hirsch et al.* do not teach a method for enhancing the transduction efficiency of a recombinant virus or for enhancing apoptosis in a tumor cell by using a relaxin-encoding nucleotide sequence operatively linked to a regulatory sequence directing its expression, where the relaxin protein expressed thereby enhances transduction efficiency or enhances apoptosis in a tumor cell. *Hirsch et al.* merely disclose relaxin as one of hundreds of potential target genes that are ***expressed by a proteasome inhibitor***, but not for the use to enhance the transduction efficiency of a delivery system or to enhance apoptosis in a tumor cell. No teaching or suggestion of the use of relaxin to enhance the transduction efficiency of a gene delivery system or to enhance apoptosis in a tumor cell is found in *Hirsch et al*.

In this regard, Applicants note the Examiner's assertion that such

properties, e.g., "enhanced efficiency" are considered functional properties inherent to the relaxin protein expressed by the gene delivery system (of *Hirsch et al.*). Applicants do not agree with the Examiner. *Hirsch et al.* do not, expressly or inherently, teach the enhancement of the transduction efficiency of a gene delivery system by the expressed relaxin protein.

As mentioned above, the method of *Hirsch et al.* necessarily requires contacting a cell or tissue with a proteasome inhibitor to express the target gene contained therein. Figures 1-5 and Examples 1-3 of *Hirsch et al.* clearly demonstrate that the expression of a target gene (i.e., mouse IL-10, luciferase, or mouse IL-4 gene) is remarkably ***enhanced by the administration of a proteasome inhibitor***, i.e., zLLL (zoxyl-L-leucyl-L-leucyl-L-leucinal) or helper virus of adenovirus; however, the expression of a target gene loaded in the recombinant AAV, ***without introduction of the proteasome inhibitor, is not shown***. In particular, it is evident from Figure 1 that an incubation of human synoviocytes with zLLL dramatically enhances the expression of mouse IL-10 transgene, which has been transduced into the synoviocytes by AAV gene transfer system. *See* paragraph [0154] of *Hirsch et al.* Also see the data in Figure 2 of *Hirsch et al.*, showing that the target gene is almost silent if its expression is not induced by the administration of zLLL (proteasome inhibitor) or Ad (helper adenovirus).

Accordingly, although *Hirsch et al.* teach that the recombinant AAV disclosed therein may contain relaxin gene, the recombinant AAV of *Hirsch et al.*

does not express the relaxin gene without introduction of proteasome inhibitors. As *Hirsch et al.* teach at paragraph [0005], "recombinant AAVs, i.e., AAVs containing foreign DNA, often do not express the foreign DNA in various tissues." This deficiency in target gene expression is attributed to the AAV system. *Hirsch et al.* teach to use proteasome inhibitors for the expression of target genes contained in the AAV system. Accordingly, the relaxin gene, if contained in the recombinant AAV of *Hirsch et al.*, does not exert such functions as required by the present claims because it cannot be expressed in the transduced cells without introduction of proteasome inhibitors. It is evident from the disclosure in *Hirsch et al.* that the recombinant AAV of *Hirsch et al.* that may contain relaxin gene as a target gene, ***does not possess the property of enhancing the transduction efficiency of the recombinant virus because the recombinant AAV itself cannot express the target gene without administration of proteasome inhibitors or helper virus of adenovirus***.

In contrast, the present subject matter is based on the fact that expressed relaxin protein can enhance the transduction efficiency of the recombinant viral vector into cells. The specification, in sections of "Evaluation on the transduction efficiency of dl-LacZ-RLX adenovirus to in vitro tumor tissue using tumor spheroids" and "Evaluation on the transduction efficiency of dl-LacZ-RLX adenovirus in tumor mass in vivo," clearly demonstrates that the relaxin-expressing recombinant adenovirus (dl-LacZ-RLX) according to the present claims is transduced and spread to the core of the tumor spheroid ***with higher***

efficiency than the control viral vector, dl-LacZ, that does not express relaxin. *See* Figures 3 and 4 submitted herewith in color.

Accordingly, Applicants submit that the method for "enhancing transduction efficiency" of the recombinant virus using the recombinant virus containing the relaxin-encoding nucleotide as recited in claim 27, as well as the method for "enhancing apoptosis" in a tumor cell using the recombinant virus containing the relaxin-encoding nucleotide as recited in claim 33, are not, inherently or expressly, anticipated by *Hirsch et al*.

In view of the foregoing, *Hirsch et al.* fail to teach each and every element/limitation of the present claims, and thus do not anticipate the present claims under 35 USC §102(b) or under 35 USC §102(e). Therefore, Applicants respectfully request the Examiner to reconsider and withdraw these rejections.

II. Rejection of Claims 22 and 24-26 under 35 USC §103(a)

The Examiner has rejected claims 22 and 24-26 as being obvious over *Hirsch et al.* in view of *Hallenbeck et al.* (US Patent No. 5,998,205) and *Dalemans et al.* (US Patent No. 6,136,594). The Examiner asserts that it would have been obvious to a skilled artisan to substitute a first adenovirus expression vector as taught by *Hirsch et al.* with a second adenovirus expression vector comprising a deletion of the E3 region into which the relaxin-encoding nucleotide is inserted, inactivation of the E1B 19 and/or E1B 55 genes, and/or an active E1A gene as taught by *Hallenbeck et al.* and *Dalemans et al.* with a reasonable

expectation of success, because such substitution of one known element for another would have yielded predictable results to the skilled artisan at the time of the invention.

As mentioned, claims 22 and 24-26 have been cancelled making this rejection moot. The subject matter of the cancelled claims is covered by new claims 32 and 36-38. Claim 32 is dependent from claim 27 and claims 36-38 are dependent from claim 33. Accordingly, Applicants respectfully traverse this rejection for all pending claims 27-38.

Applicants note that to establish a *prima facie* case of obviousness, the PTO must satisfy three requirements. First, as the U.S. Supreme Court held in *KSR International Co. v. Teleflex Inc., 550 U.S. 398 (2007)*, a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc.* v. *Chugai Pharm. Co.*, 18 USPQ 1016, 1023 (C.C.P.A 1970). Lastly, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

In the present application, a *prima facie* case of obviousness has not been established by the cited references against the presently pending claims, since the cited references, taken alone or in combination, fail to teach or suggest all the limitations of the claims, as required by *In re Wilson*.

The discussion on the present subject matter and the teachings of *Hirsch et al.,* made above in Section I, is incorporated herein in its entirety. To summarize, the presently claimed method for enhancing transduction efficiency of a recombinant virus recited in claim 27, and the method for enhancing apoptosis in a tumor cell recited in claim 33 are not anticipated by *Hirsch et al.*

Neither Hallenbeck et al. nor Dalemans et al. can remedy the deficiencies of Hirsch et al.

Hallenbeck et al. describe a targeted gene therapy using recombinant vectors, particularly replication-conditional vectors and methods for using them. *Hallenbeck et al.* has been cited by the Examiner since the reference describes recombinant adenoviral expression vectors comprising a deleted E3 region in which the gene of interest to be expressed is inserted, said vector comprises an active E1 A gene operatively linked to a heterologus, tissue-specific transcriptional regulatory sequence. *Dalemans et al.* describe a replication deficient recombinant adenovirus vector in the genome of which is inserted an expression cassette comprising the DNA fragment coding for the human CFTR protein, said DNA fragment being placed under the control of the elements for the expression thereof. This reference has been cited by the Examiner since it describes replication deficient adenovirus vectors in which the majority of E1B genes and E3 region are inactive.

However, neither of the references, *Hallenbeck et al.* and *Dalemans et al.* teaches or suggests relaxin gene itself, nor the method for enhancing

transduction efficiency of a recombinant virus or apoptosis in a tumor cell using the construction of a recombinant virus containing expressible relaxin gene. Accordingly, *Hallenbeck et al.* and *Dalemans et al.* cannot remedy the deficiencies of *Hirsch et al.*

Applicants submit that *Hirsch et al., Hallenbeck et al.* and *Dalemans et al.,* taken alone or in combination, fail to teach or suggest all the limitations of the present claims, as required by *In re Wilson*, and therefore cannot render the presently pending claims obvious within the meaning of 35 USC §103(a). Reconsideration and withdrawal of the rejection is therefore respectfully requested.

CONCLUSION

In view of the foregoing, Applicants submit that the pending claims are in condition for allowance. Early notice to this effect is earnestly solicited. The Examiner is invited to contact the undersigned attorney if it is believed such contact will expedite the prosecution of the application.

If the Examiner has any questions or comments regarding this matter, he is welcomed to contact the undersigned attorney at the below-listed number and address.

In the event this paper is not timely filed, applicants petition for an appropriate extension of time. Please charge any fee deficiency or credit any overpayment to Deposit Account No. 14-0112.

Respectfully submitted,

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